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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/104010 A1

(54) Title: CRYSTALLINE FORM OF CEFDINIR

(57) Abstract: The invention relates to a new crystalline form of cefdinir and processes for producing the crystalline cefdinir. More particularly, it relates to the preparation of new crystalline form of cefdinir, referred to as 'Form R' and pharmaceutical compositions that include the 'Form R'. It also relates to a method of treatment of infectious diseases comprising administration of the 'Form R'.

CRYSTALLINE FORM OF CEFDINIR

Field of the Invention

The field of the invention relates to a new crystalline form of cefdinir and processes for producing the crystalline cefdinir. More particularly, it relates to the preparation of new crystalline form of cefdinir, referred to as 'Form R' and pharmaceutical compositions that include the 'Form R'. It also relates to a method of treatment of infectious diseases comprising administration of the 'Form R'.

Background of the Invention

Chemically, cefdinir is 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer). Cefdinir is a very useful antimicrobial agent, and is known from U.S. Patent No. 4,559,334. Cefdinir is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum than other orally administrable antibiotics. Cefdinir is particularly effective against staphylococci and streptococci. U.S. Patent No. 4,935,507 discloses a crystalline form, i.e. Crystal A of cefdinir characterized by its specific powder X-ray diffraction pattern and infrared spectrum.

Summary of the Invention

In one general aspect there is provided a crystalline form of cefdinir, 'Form R'.

The Form R may have the X-ray diffraction pattern of Figure I, infrared spectrum of Figure II and the differential scanning calorimetry plot of Figure III.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically acceptable amount of Form R of cefdinir; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a process for the preparation of Form R of cefdinir. The process includes preparing a solution or a suspension of cefdinir or a salt thereof in water; acidifying the solution or suspension to get a mixture; stirring the mixture for a time sufficient to precipitate the crystalline Form R of cefdinir; and recovering the cefdinir in the crystalline Form R.

Recovering the cefdinir in the crystalline Form R includes one or more of filtration, filtration under vacuum, decantation and centrifugation.

The process may include further drying of the product so obtained.

The process may produce the cefdinir in the crystalline Form R having a water of hydration of at least 4%. In particular, the Form R may be a monohydrate of cefdinir.

In another general aspect there is provided a method of treating microbial infections in a warm-blooded animal, the method comprising providing a pharmaceutical composition to the warm-blooded animal that includes Form R of cefdinir.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Description of the Drawings

Figure 1 is X- ray powder diffraction pattern of Form R of cefdinir.

Figure 2 is an infrared spectrum in KBr of Form R of cefdinir.

Figure 3 is differential scanning calorimetry plot of Form R of cefdinir.

Detailed Description of the Invention

The inventors have found new crystalline form of cefdinir, referred to as 'Form R'. The new crystalline form is characterized by its X-ray powder diffraction pattern as shown in Figure 1 infrared spectrum as shown in Figure 2 and differential scanning calorimetry plot as shown in Figure 3. The inventors also have developed process for the preparation of the new crystalline form of cefdinir, by preparing a solution or a suspension of cefdinir or a salt thereof; acidifying the solution or suspension to get a mixture; stirring the mixture for a time sufficient to precipitate the crystalline Form R of cefdinir; and recovering the cefdinir in the crystalline Form R. The inventors also have developed pharmaceutical composition that contain Form R of the cefdinir, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In general crystalline Form R of cefdinir is characterized by X-ray peaks at about 11.72, 18.58, 20.92, 21.2, 22.28, 24.42, and 26.24 degrees two-theta and infrared spectral bands at about 1015, 1049, 1135, 1190, 1350, 1543, 1610, and 1667 cm^{-1}.

In general, the solution or suspension of cefdinir may be obtained by dissolving cefdinir or a salt thereof in water. Alternatively, such a solution may be obtained directly from a reaction in which cefdinir is formed.

The process for preparing crystalline form R of cefdinir can be carried out at a temperature of about 10 °C or lower temperatures, for example from about 10 °C to about -10 °C. More particularly, it can be carried out at a temperature from about 5 °C to about -5°C.

The acidification process can be carried out by adding an inorganic or an organic acid. Examples of suitable acids include inorganic acids such as hydrochloric, sulfuric, phosphoric and nitric acids, and organic acids such as trifluoroacetic, methanesulfonic, benzenesulfonic, p-toluenesulfonic, and formic acids.

The acid is added in an amount that makes the pH value of the solution/suspension from about 0.5 to about 4, for example, from about 1.5 to about 3.

The concentration of the solution/suspension of the salt of cefdinir can be in the range from about 1% to about 20% by weight, for example, from about 3% to about 10% by weight.

After acidification, the mixture may be stirred for a time sufficient to precipitate crystalline Form R of cefdinir. The duration can be from about 1 hour to about 15 hours in general and may vary depending on the temperature, the concentration, as also whether the starting salt is in solution or suspension. The precipitation of the crystalline Form R from a solution may require stirring for a longer duration in general, for example from about 5 hours to about 15 hours.

Suitable salts of cefdinir that can be used in the process are conventional non-toxic salts and may include a salt with an inorganic base, for example an alkali metal salt, such as sodium and potassium salts; an alkaline earth metal salt, such as calcium and magnesium salts; an ammonium salt; a salt with an organic base, for example, an organic amine salt such

as, triethylamine, pyridine, picoline, ethanolamine, triethanolamine, and dicyclohexylamine salts.

The salts of cefdinir may be obtained by methods known in the art including those described in U.S. Patent No. 4,559,334. In particular, the crystalline potassium salt of cefdinir was prepared according to the process disclosed in our co-pending PCT Patent Application Serial No. PCT/IB02/05315.

The salts of cefdinir may also be obtained by adding a base to a suspension of cefdinir in water. Examples of bases include alkali metal salts of carboxylic acids, such as sodium acetate and potassium acetate; organic amines, such as triethylamine, pyridine, picoline, ethanolamine, triethanolamine, dicyclohexylamine, ammonium hydroxide, alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide, alkali metal carbonates, such as sodium carbonate or potassium carbonate, and alkali metal bicarbonates, such as sodium bicarbonate.

Cefdinir may be prepared using the reactions and techniques known in the art including those described in U.S. Patent Nos. 4,559,334; 4,870,168; and 6,093,814; WO 92/7840; and PCT Patent Application Serial No. PCT/IB02/01410.

The precipitated crystalline Form R of cefdinir may be recovered by conventional methods such as filtration, filtration under vacuum, decantation and centrifugation.

The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

The crystalline Form R of cefdinir is pure, easy to handle, stable against heat and light, and is at least as free of residual solvents as the starting cefdinir. It is thus, suitable for pharmaceutical preparations and in storage.

The cefdinir of crystalline Form R can be administered for the treatment of microbial infections, such as skin respiratory and urinary tract infections in a warm-blooded animal. In particular, cefdinir of crystalline Form R may be used for treating community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The cefdinir Form R can be administered by any conventional means alone or in combination with other therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected in the basis of the chosen route of administration and standard pharmaceutical practice.

The cefdinir Form R may be formulated into ordinary dosage forms such as, for example, tablets, capsules, suspensions, dispersions, injectables and other pharmaceutical forms. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The compositions include dosage forms suitable for oral, buccal, rectal, and parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The oral dosage forms may include solid dosage forms, like powder, tablets, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions, emulsions, pastes and elixirs. Parenteral dosage forms may include intravenous infusions, sterile solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be reconstituted with sterile water for parenteral administration, and the like.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and are not intended to limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Methods

X-Ray Powder Diffraction

X-ray powder diffraction patterns were recorded using the following instrument and parameters:

X-Ray Difractometer, Rigaku Coorperation, RU-H3R

Goniorneter CN2155A3

X-Ray tube with Cu target anode

Divergence slits 1 0, Receiving slit 0.15mm, Scatter slit 1 0

Power: 40 KV, 100 mA

Scanning speed: 2 deg/min step: 0.02 deg

Wave length: 1.5406 A

Infrared Spectra

Infrared spectra were recorded using the following instrument and parameters:

Instrument:Perkin Elmer,16 PC

SCAN: 16 scans, 4.0 cm^{-1}

According to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

Differential Scanning Calorimetry

Differential scanning calorimetry plots were recorded using the following instrument and parameters:

DSC821 e, Mettler Toledo

Sample weight: 3-5 mg

Temperature range: 25-100° C

Heating rate: 1° C/min

Nitrogen 80.0 mL/min

Number of holes in the crucible: 1

Example 1

Crystalline cefdinir potassium salt (5.0 g) was suspended in water (150ml) at 3 – 4°C. pH of this heterogeneous mixture was adjusted to 2.4 to 2.6 at 3 to 4°C using 3N hydrochloric acid. The mixture was stirred for 5 to 6 hours maintaining temperature at 3 to 4°C. The precipitated solid was filtered and dried under vacuum at 40 to 45°C to get 4.0 g of off-white crystalline Form R of cefdinir.

HPLC Purity = 99.59 %, Moisture Content (% w/w by KF) = 4.55 %.

XRD, IR, and DSC spectra were similar to those shown in Figure I, II and III, respectively.

Example 2

Cefdinir free acid (5.0 g) was suspended in water at ambient temperature. pH of this heterogeneous mixture was adjusted to 6.0 to 6.5 with sodium bicarbonate for complete dissolution. Undissolved particulate matter was filtered off. The clear solution was cooled to 2 to 5°C. pH was adjusted to isoelectric point of cefdinir with 3N hydrochloric acid at 2 to 5°C. The mixture was stirred for 8 to 10 hours maintaining temperature at 2 to 5°C to grow form R of cefdinir. The precipitated solid was filtered and dried under vacuum at 40 to 45°C to get 3.8 g of off-white crystalline Form R of cefdinir.

HPLC Purity = 99.15 %, Moisture Content (% w/w by KF) = 6.19 %.

XRD, IR, and DSC spectra were similar to those shown in Figure I, II and III, respectively.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. 'Form R' crystalline cefdinir.

2. The Form R of claim 1, wherein the cefdinir has the X-ray diffraction pattern of Figure 1.

3. The Form R of claim 1, wherein the cefdinir has the infrared spectrum of Figure 2.

4. The Form R of claim 1, wherein the cefdinir has the differential scanning calorimetry plot of Figure 3.

5. The Form R of claim 1, which is an off-white crystalline powder.

6. A crystalline Form R of cefdinir characterized by X-ray diffraction pattern having peaks at about 11.72, 18.58, 20.92, 21.2, 22.28, 24.42, and 26.24 degrees 2-theta.

7. A crystalline Form R of cefdinir characterized by infrared spectral bands at about 1015, 1049, 1135, 1190, 1350, 1543, 1610, and 1667 cm^{-1}.

8. A crystalline Form R of cefdinir, characterized by a water of hydration of at least 4%.

9. The crystalline form of claim 8, which is a monohydrate of cefdinir.

10. A pharmaceutical composition comprising:

a therapeutically effective amount of Form R cefdinir;

and one or more pharmaceutically acceptable carriers, excipients or diluents.

11. The pharmaceutical composition of claim 10, wherein the cefdinir has the X-ray diffraction pattern of Figure 1.

12. The pharmaceutical composition of claim 10, wherein the cefdinir has the infrared spectrum of Figure 2.

13. The pharmaceutical composition of claim 10, wherein the cefdinir has the differential scanning calorimetry plot of Figure 3.

14. A process for the preparation of crystalline Form R of cefdinir, the process comprising:

preparing a solution or a suspension of cefdinir or a salt thereof in water;

acidifying the solution or suspension at a temperature of from about -10°C to about 10°C to get a mixture;

stirring the mixture for a time sufficient to precipitate the crystalline Form R; and

recovering the cefdinir in the crystalline Form R.

15. The process of claim 14, wherein the temperature is from about -5°C to about 5°C.

16. The process of claim 14, wherein the solution or suspension is acidified to a pH value of from about 0.5 to about 4.

17. The process of claim 16, wherein the pH value is from about 1.5 to about 3.

18. The process of claim 14, wherein the salt of cefdinir is obtained by adding a base to a suspension of cefdinir in water.

19. The process of claim 14 or 18, wherein cefdinir or its salt is obtained as a solution directly from a reaction in which cefdinir is formed.

20. The process of claim 14, wherein the salt of cefdinir is a salt with an inorganic base.

21. The process of claim 20, wherein the salt is an alkali metal salt, an alkaline earth metal salt or an ammonium salt.

22. The process of claim 21, wherein the alkali metal salt is a sodium or potassium salt.

23. The process of claim 14, wherein the salt of cefdinir is a salt with an organic base.

24. The process of claim 23, wherein the salt is a triethylamine, pyridine, picoline, ethanolamine, triethanolamine, or dicyclohexylamine salt of cefdinir.

25. The process of claim 14, further comprising additional drying of the product obtained.

26. The process of claim 14, further comprising forming the product obtained into a finished dosage form.

27. The process of claim 14, wherein the cefdinir has the X-ray diffraction pattern of Figure 1.

28. The process of claim 14, wherein the cefdinir has the infrared spectrum of Figure 2.

29. The process of claim 14, wherein the cefdinir has the differential scanning calorimetry plot of Figure 3.

30. A method for treating microbial infections in a warm-blooded animal comprising administering a pharmaceutical composition that includes a crystalline Form R of cefdinir.

31. The method of claim 30, wherein the microbial infection is a skin respiratory or a urinary tract infection.

32. The method of claim 30, wherein the microbial infection is a community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infection.

Figure I

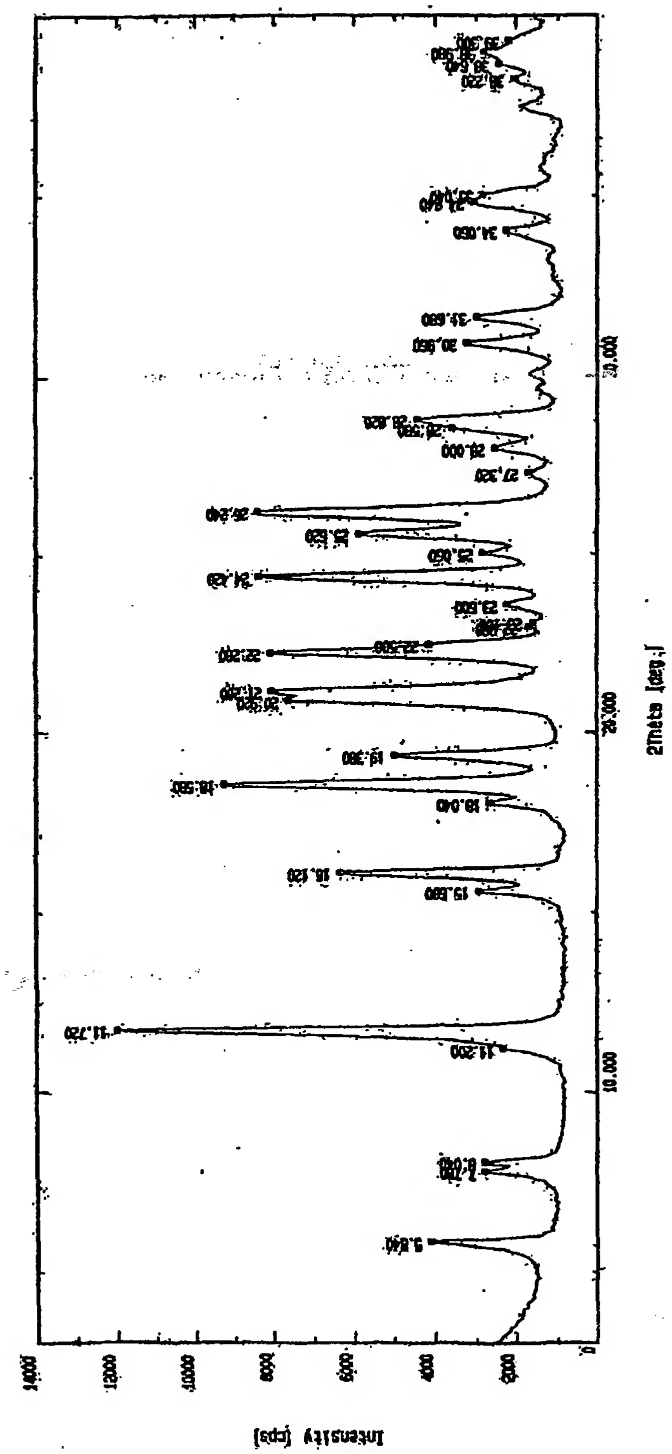

Figure II

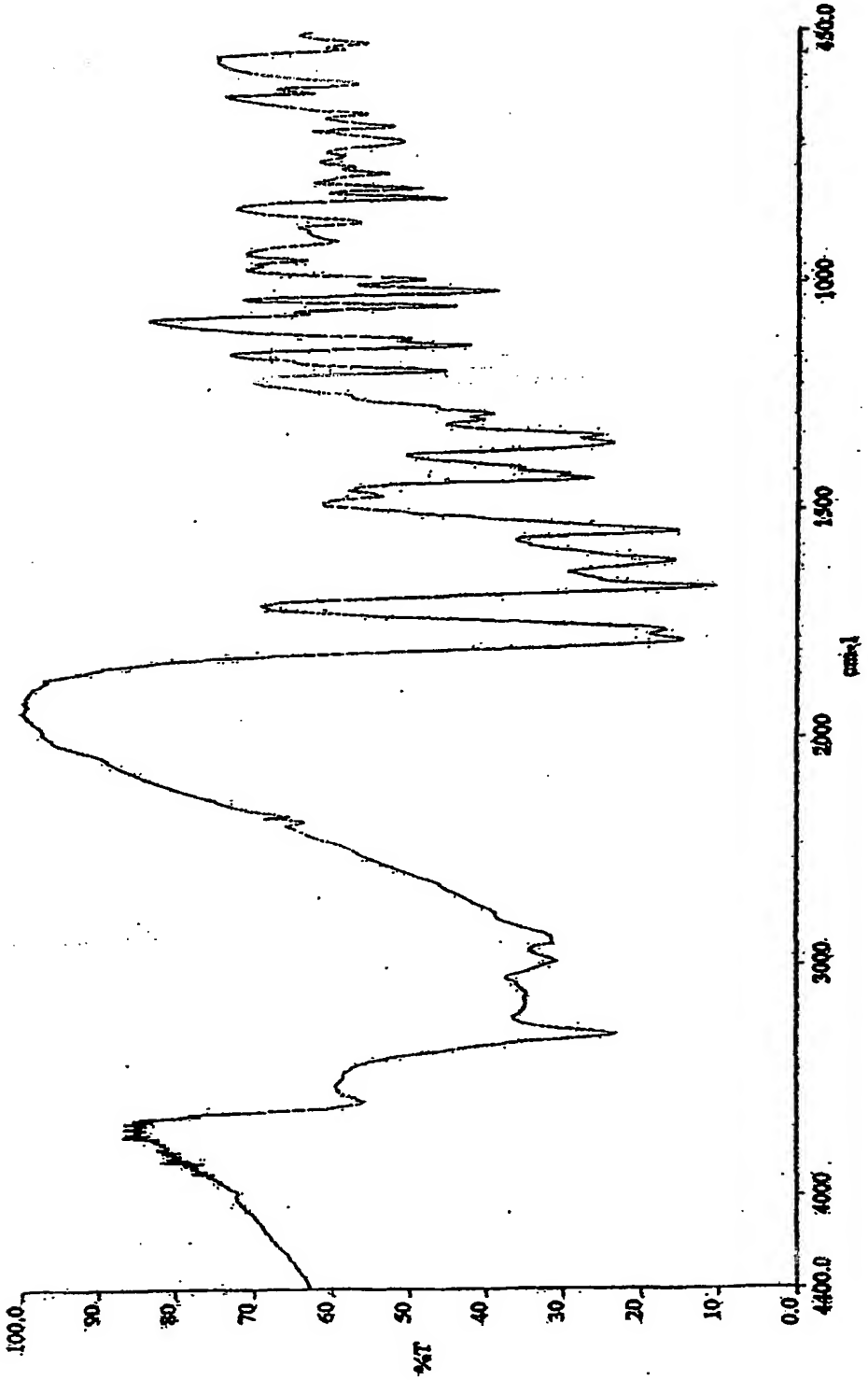
100.0
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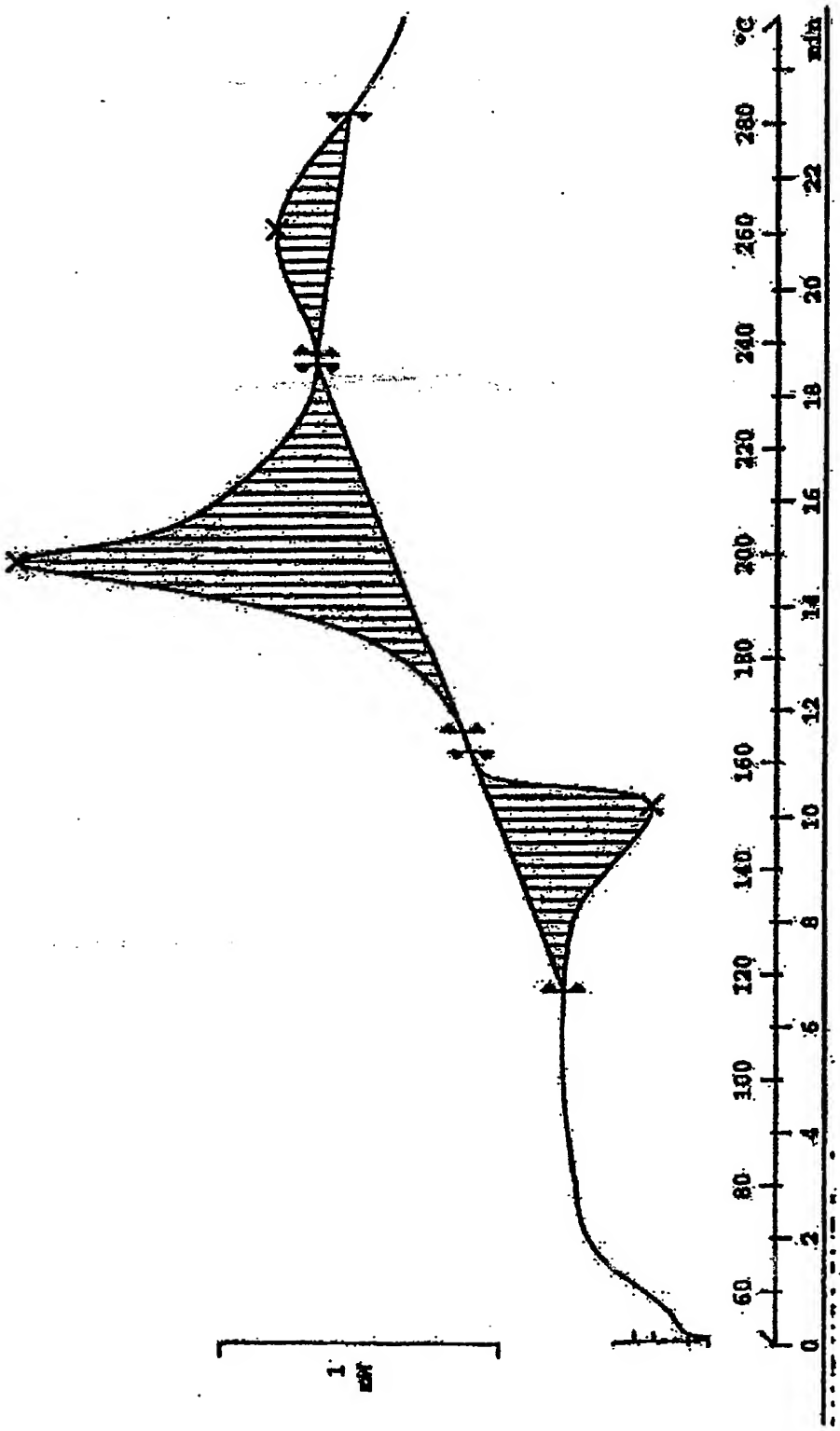
Figure III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240
220
200
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120
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INTERNATIONAL SEARCH REPORT

Interna...pplication No
PCT/IB2004/001629

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/22 A61K31/546 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 559 334 A (KAWABATA KOHJI ET AL) 17 December 1985 (1985-12-17) cited in the application Examples 14 and 16.	1-32
X	US 4 935 507 A (TAKAYA TAKAO ET AL) 19 June 1990 (1990-06-19) cited in the application Abstract; column 1, lines 20-28; examples 1-5.	1-32
X	US 6 093 814 A (CHUN JONG PIL ET AL) 25 July 2000 (2000-07-25) cited in the application Abstract; examples 6 and 8.	1-32

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2004	25/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

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INTERNATIONAL SEARCH REPORT

Internatic ...lication No
PCT/IB2004/001629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 350 869 B1 (STURM HUBERT ET AL) 26 February 2002 (2002-02-26) Abstract; examples 2 and 3.	1-32
X	EP 1 273 587 A (OTSUKA KAGAKU KK) 8 January 2003 (2003-01-08) Abstract; example 1.	1-32
X	WO 02/098884 A (CHANG YOUNG KIL ; KIM CHEOL KYUNG (KR); KIM HONG SUN (KR); LEE GWAN SU) 12 December 2002 (2002-12-12) Abstract; examples 3 and 4.	1-32
P,X	WO 03/050124 A (KUMAR NEELA PRAVEEN ; KUMAR YATENDRA (IN); PRASAD ASHOK (IN); PRASAD M) 19 June 2003 (2003-06-19) Abstract; example 4.	1-32
E	WO 2004/056835 A (MARTIN GOMEZ PATRICIO ; ALPEGIANI MARCO (IT); CABRI WALTER (IT); POZZI) 8 July 2004 (2004-07-08) Abstract; example 5.	1-32
X	PATENT ABSTRACTS OF JAPAN vol. 0141, no. 26 (C-0699), 9 March 1990 (1990-03-09) & JP 2 000790 A (FUJISAWA PHARMACEUT CO LTD), 5 January 1990 (1990-01-05) abstract	1-32
P,X	GONZÀLEZ, M. ET AL.: "An alterntive procedure for preparation of cefdinir" IL FARMACO, vol. 58, no. 6, June 2003 (2003-06), pages 409-418, XP001182681 Page 417, last paragraph.	1-32
L	CAIRA, M. R.: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS" TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1998, pages 163-208, XP001156954 ISSN: 0340-1022 Page 164, paragraph 1; page 165, paragraph 2; and page 165, last paragraph to page 166, first paragraph; cited as common general knowledge.	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001629

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/001629

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4559334 A	17-12-1985	AT 381497 B	27-10-1986
		AT 342783 A	15-03-1986
		AT 385994 B	10-06-1988
		AU 576735 B2	08-09-1988
		AU 1927783 A	05-04-1984
		CA 1206956 A1	01-07-1986
		CH 657857 A5	30-09-1986
		DE 3379463 D1	27-04-1989
		DK 427083 A ,B,	31-03-1984
		EP 0105459 A2	18-04-1984
		ES 8600309 A1	01-01-1986
		ES 8800235 A1	01-01-1988
		FI 833370 A ,B,	31-03-1984
		FR 2533926 A1	06-04-1984
		GB 2127812 A ,B	18-04-1984
		GR 79674 A1	31-10-1984
		HU 190166 B	28-08-1986
		IE 56046 B1	27-03-1991
		IT 1173673 B	24-06-1987
		JP 1926846 C	25-04-1995
		JP 6057713 B	03-08-1994
		JP 62294687 A	22-12-1987
		KR 9103118 B1	18-05-1991
		MY 87487 A	31-12-1987
		NO 833531 A ,B,	02-04-1984
		PH 20022 A	01-09-1986
		PT 77426 A ,B	01-10-1983
		SG 61387 G	04-03-1988
		SU 1309911 A3	07-05-1987
US 4935507 A	19-06-1990	AT 123221 T	15-06-1995
		AU 617347 B2	28-11-1991
		CA 1297096 C	10-03-1992
		DE 3853901 D1	06-07-1995
		DE 3853901 T2	12-10-1995
		EP 0304019 A2	22-02-1989
		ES 2072856 T3	01-08-1995
		HK 18496 A	09-02-1996
		IE 67348 B1	20-03-1996
		JP 1250384 A	05-10-1989
		JP 1943842 C	23-06-1995
		JP 6074276 B	21-09-1994
		KR 9708126 B1	21-05-1997
		MX 9203468 A1	01-09-1992
		ZA 8805709 A	26-04-1989
US 6093814 A	25-07-2000	KR 174432 B1	18-02-1999
		KR 174431 B1	18-02-1999
		AT 218572 T	15-06-2002
		DE 69621649 D1	11-07-2002
		DE 69621649 T2	19-09-2002
		DK 874853 T3	23-09-2002
		EP 0874853 A1	04-11-1998
		ES 2175167 T3	16-11-2002
		JP 2000502700 T	07-03-2000
		WO 9724358 A1	10-07-1997
		PT 874853 T	30-09-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/001629

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6350869 B1	26-02-2002	AT 405283 B	25-06-1999
		AT 57097 A	15-11-1998
		AT 244249 T	15-07-2003
		AU 731413 B2	29-03-2001
		AU 7428898 A	30-10-1998
		BR 9809745 A	20-06-2000
		CA 2283718 A1	15-10-1998
		CN 1139596 C	25-02-2004
		DE 69816056 D1	07-08-2003
		DE 69816056 T2	15-04-2004
		WO 9845299 A1	15-10-1998
		EP 0973779 A1	26-01-2000
		HU 0002987 A2	28-02-2001
		ID 22536 A	04-11-1999
		JP 3421354 B2	30-06-2003
		JP 2000514833 T	07-11-2000
		NO 994466 A	15-09-1999
		PL 335620 A1	08-05-2000
		SK 134399 A3	16-05-2000
		TR 9902406 T2	21-02-2000
EP 1273587 A	08-01-2003	JP 2001294590 A	23-10-2001
		EP 1273587 A1	08-01-2003
		CN 1134445 B	14-01-2004
		WO 0179211 A1	25-10-2001
WO 02098884 A	12-12-2002	KR 2002092612 A	12-12-2002
		EP 1392703 A1	03-03-2004
		WO 02098884 A1	12-12-2002
WO 03050124 A	19-06-2003	WO 03050124 A1	19-06-2003
WO 2004056835 A	08-07-2004	WO 2004056835 A1	08-07-2004
JP 2000790 A	05-01-1990	ES 2013828 A6	01-06-1990
		JP 2600878 B2	16-04-1997
		KR 140887 B1	01-06-1998